REMARKS

Claims 1-18 and 20-28 are pending in the application. Claims 19 and 29-41 have been cancelled. Claims 1-18 and 20-28 have been rejected. Claims 1-18 and 20-28 have been amended. Amendments to the claims contain no new matter. Therefore, Applicants respectfully request entry of the Amendment.

DRAWINGS-INFORMALITIES

The Examiner has objected to the following informalities in the drawings:

1. Figures 1 and 15 are incorrectly numbered.
2. Figure 1 does not include a region wherein a part of the depicted structure is indicated in "bold" letters as alleged on page 46.

In response, Applicants have herein amended the drawings to address the Examiner's objections. Accordingly, Applicants respectfully request withdrawal of the objections.

SPECIFICATION-INFORMALITIES

The Examiner has objected to the following informalities in the specification:

1. The first paragraph of the specification does not provide information on the prior application(s).

2. The specification lacks the title "Brief Description of the Drawings" on page 18.

3. The panels of Figures 1, 3, 5, 6, 7, and 15 are not referred to in the specification

4. The subject specification uses trademark recitations without the symbol "®".

In response, Applicants have herein amended the specification to address the Examiner's objections. Accordingly, Applicants respectfully request withdrawal of the objections.

PRIORITY REJECTIONS

The Examiner rejected Applicants' claim to priority from U.S. Provisional Applications 60/196,305, filed 4/12/00 and 60/156,940, filed 09/30/99, alleging that the specification of these provisional applications lacks enabling disclosure for a "vaccine" that elicits functional antibodies and that prevents or treats the variously recited diseases.

Applicants traverse the Examiner's rejection. Applicants contend that U.S. Provisional Application 60/156,940, filed 09/30/99 (pages 4 and 17-21, attached hereto as Exhibit A) demonstrates an epitope, comprising a PEtn residue on the 3-position of HepII (page 4 first full paragraph, lines 3-5) which generated opsonic antibodies directed against 70% of over 100 representative *N. meningitidis* strains, representing all capsular serogroups and a variety of strains of other *Neisseria* species, (paragraph beginning on page 17, lines 1-3; first full paragraph on page 18, lines 1-3; paragraph beginning on page 20, lines 13-17); and (b) discloses vaccines comprising a PEtn residue on the 6 or 7-position of HepII (paragraph beginning on page 18, lines 17-19). Therefore, contrary to the Examiner's assertion, the provisional application is enabling to one skilled in the art for a vaccine for the treatment of disease caused by pathogenic *Neisseria*, comprising an epitope on the *Neisseria* LPS inner core characterized by the presence of a phosphoethanolamine moiety linked to a 3, 6, 7, or a combination thereof, position of HepII of the inner core, wherein said vaccine elicits protective and/or immunoprophylactic antibodies against a majority of pathogenic Neisseria strains, as recited in the amended claims. In addition, U.S. Provisional Application 60/196,305, filed 4/12/00, further elaborates upon the findings of U.S. Provisional Application 60/156,940, by providing further characterizing antibodies that recognize a PEtn

residue on the 6 or 7-position of HepII. Accordingly, Applicants respectfully request that the Examiner withdraw the objection and grant claims of the subject application a priority of U.S. Provisional Applications 60/196,305 and 60/156,940.

CLAIM REJECTIONS - 35 U.S.C. § 112, FIRST PARAGRAPH

In the Office Action, the Examiner has rejected claims 1-18 and 20-28 under 35 U.S.C. § 112, first paragraph, stating that Applicants' deposit of a hybridoma producing the B5 monoclonal antibody has not satisfied the provisions of the Budapest Treaty.

In response, Applicants have attached hereto a signed depository receipt for the hybridoma producing the B5 monoclonal antibody. Applicants hereby affirm that the deposited cell line is the same as described in the specification. Accordingly, Applicants respectfully request withdrawal of the rejection.

The Examiner further rejected claims 1-18 and 20-28 under 35 U.S.C. § 112, first paragraph as allegedly failing to convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of a vaccine therapeutically or prophylactically functional or effective in curing or preventing systemic or local meningococcal or gonococcal infections, as broadly claimed.

Further, the Examiner admitted that the specification is enabling for: 1) an immunogenic composition comprising a formalin-killed whole cell vaccine of a *galE* mutant of *Neisseria meningitidis* which on active immunization elicits antibodies reactive with the LPS inner core of said *galE* mutant and a Neisserial inner core LPS epitope containing phosphatidylethanolamine (hereinafter referred to as "PeTN") at position 3 of HepII; 2) antibodies bactericidal against the homologous *galE* mutant of *Neisseria meningitidis*.

In order to expedite prosecution, Applicants have herein amended claims 1-18 and 20-28 to be directed to a vaccine for the treatment of disease caused by pathogenic *Neisseria*, comprising an immunogenic component, the immunogenic component being an epitope on

the *Neisseria* lipopolysaccharide (hereinbelow referred to as "LPS") inner core characterized by the presence of a phosphoethanolamine moiety linked to a 3, 6, 7, or a combination thereof, position of HepII of the inner core, wherein said vaccine elicits protective and/or immunoprophylactic antibodies against a majority of pathogenic Neisseria strains.

Applicants submit that the subject application demonstrates an epitope, which comprises an epitope on the *Neisseria* LPS inner core characterized by the presence of a phosphoethanolamine moiety linked to a 3, 6, 7, or a combination thereof, position of HepII of the inner core. The application further demonstrates that antibodies elicited by the epitope (a) recognized 70% of a collection of over 100 representative *N. meningitidis* strains, representing all capsular serogroups; and a variety of strains of other *Neisseria* species, (b) are opsonic and bactericidal; and (c) reduce bacteremia when administered to naïve hosts challenged with *N. meningitidis*. One skilled in the art would therefore understand such a disclosure to be enabling for a vaccine for the treatment of pathogenic *Neisseria*. Specifically, one skilled in the art would, in view of the disclosure presented, find the disclosure enabling for a vaccine for the treatment of disease caused by pathogenic *Neisseria*, comprising an epitope on the *Neisseria* LPS inner core characterized by the presence of a phosphoethanolamine moiety linked to a 3, 6, 7, or a combination thereof, position of HepII of the inner core. Further, one skilled in the art would appreciate that the vaccine would elicit protective and/or immunoprophylactic antibodies against a majority of pathogenic *Neisseria* strains, in view of the disclosure presented. Accordingly, Applicants respectfully request withdrawal of the rejection.

The Examiner has further rejected claims 1-18 and 20-28 under 35 U.S.C. § 112, first paragraph, for claiming a vaccine eliciting antibodies against a majority of strains of pathogenic *Neisseria*, or against at least 60%, 70%, 85% or 95% of the strains, alleging that the species of pathogenic *Neisseria* encompassed in the limitation includes "an infinite number of strains of pathogenic *Neisseria*, including those yet to be discovered" (Office Action, page 6).

In response, Applicants respectfully traverse the Examiner's rejection. Applicants maintain that the subject application has provided one skilled in the art sufficient written description and enabling disclosure for a vaccine eliciting antibodies against a majority of strains of pathogenic *Neisseria*. "The written description requirement for a claimed genus may be satisfied through sufficient description of ***a representative number of species*** by actual reduction to practice" (Manual of Patent Examining Procedure, Section 263, page 2100-168; emphasis added). Applicants submitted in Table 2 (pages 41-42) a list of more than 10 genetically diverse key pathogenic Neisseria species that were tested for reactivity to monoclonal antibody (hereinbelow referred to as "MAb") B5. Accordingly, Applicants respectfully request withdrawal of the rejection.

Further, the Examiner has alleged under 35 U.S.C. § 112, first paragraph, that claim 24, directed to a vaccine for the prevention of meningitis, septicaemia or pneumonia or other manifestation of systemic or local disease occasioned by *Neisseria meningitidis*, is not enabled for the claimed invention. In response, in order to expedite prosecution, Applicants have herein amended claim 24 to read "treatment" instead of "prevention." Applicants submit that amended claim 24 therefore obviates the Examiner's rejection, and accordingly request that the Examiner withdraw the rejection.

Further, the Examiner has alleged under 35 U.S.C. § 112, first paragraph, that claims 1-18 and 20-28, directed to vaccine for the treatment of disease caused by pathogenic *Neisseria*, is not enabled for the claimed invention, alleging that the B5 monoclonal antibody is not elicited by a vaccine comprising the isolated LPS inner core immunogenic component (Office Action, page 7). The Examiner admitted, however, that the specification shows 1). that the B5 MAb is elicited by immunizing mice with a *galE N. meningitidis* mutant; 2). that "the reactivity of the B5 monoclonal antibody with a cross-reactive epitope on the LPS of the majority of naturally occurring, but genetically diverse strains of *N. meningitides*"; and shows 3). a "method of evaluating the cross-reactivity and the binding functions of a monoclonal antibody, B5."

Based on the foregoing, one skilled in the art would have a reasonable expectation of success, without undue experimentation, that a). the B5 MAb would be elicited by a vaccine comprising the LPS inner core immunogenic component recited in claims 1-18 and 20-28; and b) said vaccine would be effective against the majority of naturally occurring, but genetically diverse strains of *N. meningitidis.*

Further, the Examiner alleged under 35 U.S.C. § 112, first paragraph, that claims 1-18 and 20-28, are not enabling for a vaccine for the treatment of disease caused by pathogenic *Neisseria.* The Examiner cited pages 31-35 of the specification, which describe future studies to further develop the vaccine of the claimed invention, as evidence that the claimed invention has not been enabled.

Applicants respectfully traverse the rejection. Applicants statements of future studies are directed to the safety and immunogenicity of ***conjugated*** LPS. By contrast, it is understood that Applicants have taught and demonstrated immunogenicity of the epitope claimed in amended claims 1-18 and 20-28. Clearly, a person skilled in the art could practice the claimed invention without undue experimentation, especially given that the methods of testing immunogenicity of the vaccine are disclosed in the subject application.

Moreover, the subject application demonstrated that 1) antibodies elicited by the claimed vaccine bind complement (Example 3, page 57) and are both protective and bactericidal both ***in vivo*** (passive protection experiment, pages 53 and 57-58) and in a biologically relevant model system (page 30, first full paragraph, lines 4-6); and 2) phase variation does not affect recognition by the elicited antibodies (page 34, third full paragraph). Accordingly, Applicants respectfully request withdrawal of the rejection.

Further, the Examiner alleged under 35 U.S.C. § 112, first paragraph, that the subject application is not enabling for a protective vaccine against a majority of meningococcal strains or strains of *N. gonorrhoeae.* Applicants respectfully disagree. The subject application demonstrated that the B5 MAb reacts against 1) 70% of 100 representative *N. meningitidis* strains of all multiple serogroups; and 2) several strains of *N.*

gonorrhoeae (paragraph beginning on page 32, line 2, and first full paragraph of page 33). In combination with the demonstration that the B5 MAb is both protective and bactericidal, as described hereinabove, one skilled in the art would reasonably expect that the B5 MAb would protect against a majority of meningococcal strains and *N. gonorrhoeae*. Accordingly, Applicants respectfully request withdrawal of the rejection.

CLAIM REJECTIONS - 35 U.S.C. § 112, SECOND PARAGRAPH

In the Office Action, the Examiner rejected claims 1-18 and 20-28 under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter of the invention.

In response, Applicants have herein amended claims 1-18 and 20-28 to address the Examiner's typographic or clerical objections. It is respectfully asserted that the foregoing amendment merely addresses matters of form and does not change the literal scope of the claim in any way or result in any prosecution history estoppel.

Further, the Examiner objected to claim 4 under 35 U.S.C. § 112, second paragraph, for use of the following language as vague and indefinite: "substantially free from outer core" in claim 4.

Applicants submit that the definition of the term "substantially free" (from outer core LPS) is well known to those skilled in the art to denote low to undetectable levels of outer core LPS, using standard detection assays. Accordingly, Applicants respectfully request withdrawal of the rejection.

Applicants respectfully assert that these amendments render claims 1-18 and 20-28 proper under 35 U.S.C. § 112, and request that the rejections be withdrawn.

CLAIM REJECTIONS - 35 U.S.C. § 102

In the Office Action, the Examiner rejected claims 1-12, 14-18, and 20-26 under 35 U.S.C. § 102(b), as being anticipated by Arumugham et al (EP 0941738). The Examiner alleged that Arumugham disclosed a vaccine comprising a conserved inner core portion of a Gram negative bacteria, capable of eliciting antibodies that are cross-reactive with heterologous strains of said Gram negative bacteria.

Applicants respectfully disagree. The LPS claimed by Arumugham differs from that claimed in the subject application in that the LPS of the subject application comprises a glucose residue attached to HepI, which is not present in the LPS of the Arumugham vaccine. Thus, Arumugham clearly does not anticipate the claimed matter of the subject application, as it does not contain every element of the claim.

Further, Applicants' claimed immunogenic component consists of an epitope on the *Neisseria* LPS inner core characterized by the presence of a PEtn moiety linked to a 3, 6, 7, or a combination thereof, position of HepII of inner core LPS. By contrast, Arumugham states that the immunogenic component "comprises at least the conserved inner core and the lipid A portion of the LPS" (page 3, lines 35-37), and thus the epitope differs from that of the subject application.

Moreover, Arumugham states that the PEtn moiety is not necessary for protection from Gram negative bacteria:

> "The phosphates, ***phosphoethanolamine*** and pyrophosphoethanolamine groups which may be contained in the inner core may also be included in the

"conserved portion", ***although they may not be necessary***" (page 4, lines 27-29; emphasis added).

The Arumugham vaccine is also conjugated to a carrier protein, with conjugation occurring at multiple residues of the LPS inner core, which will necessarily result in masking of the claimed immunogenic component of the subject application- hence the two vaccines are not comparable. Accordingly, Arumugham does not anticipate claims directed to a vaccine for the treatment of disease caused by pathogenic *Neisseria*, comprising an epitope on the *Neisseria* LPS inner core characterized by the presence of a PEtn moiety linked to a 3, 6, 7, or a combination thereof, position of HepII of the inner core.

The Examiner used Carbonetti et al (US 5,736,361) as a basis for the demonstration that that every element of the claimed subject matter is present in Arumugham, specifically that antibodies elicited by outer membrane proteins are opsonic. Applicants respectfully disagree. Antibodies must be empirically tested to show that they are opsonic and/or protective, as stated by the Examiner (Office Action, page 8). Thus, Carbonetti does not serve to show that every element of the claimed subject matter is present in Arumugham, and, by reasoning presented above, Arumugham does not anticipate claims of the subject application. Accordingly, Applicants respectfully request withdrawal of the rejection.

The Examiner rejected claims 1, 27, and 28 under 35 U.S.C. § 102(b), as being anticipated by Kim et al (*Infect. Immun* 56: 2631-2638). The Examiner alleged that Kim disclosed *N. lactamica* lipooligosaccharide preparations which elicit antibodies cross-reactive with some *Neisseria* strains, and which may be used as vaccines, therefore anticipating Applicants' claims to a vaccine for pathogenic *Neisseria*, comprising an immunogenic component based on the inner core of an *Neisseria* LPS.

Applicants respectfully disagree. Applicants claim an immunogenic component that consists of an epitope on the *Neisseria* LPS inner core characterized by the presence of a PEtn moiety linked to a 3, 6, 7, or a combination thereof, position of HepII of inner core LPS. Kim does not demonstrate that their immunogenic component contains a PEtn moiety.

Further, Kim does not demonstrate that their immunogenic component is in the inner core LPS as opposed to the outer core LPS, lipid A, and O-specific polysaccharide chain regions also present in their preparations. Therefore, Kim does not disclose Applicants' claimed immunogenic component. Moreover, Kim did not show that antibodies elicited by their preparations are opsonic, bactericidal or in any way protective. Thus, it is not credible, based on Kim, that a vaccine comprising a phosphoethanolamine moiety linked to a 3, 6, 7, or a combination thereof, position of HepII of the inner core, is useful for the treatment of disease caused by pathogenic *Neisseria*. Thus, Kim does not anticipate the subject application. Accordingly, Applicants respectfully request withdrawal of the rejection.

The Examiner rejected claims 1-18 and 20-25 under 35 U.S.C. § 102(b), as being anticipated by Plested et al (*Infect. Immun* 67: 5417-26). As described above, the subject application claims priority from U.S. Provisional Application 60/156,940, filed 9/30/99, which precedes the October 1999 publication date of Plested. Accordingly, Plested et al is not an appropriate 35 U.S.C. § 102(b) reference, and Applicants respectfully request withdrawal of the rejection.

The Examiner rejected claims 1, 27, and 28 under 35 U.S.C. § 102(b), as being anticipated by Verheul et al (*Infect. Immun* 59: 843-51), which allegedly discloses *N. meningitidis* LPS-containing oligosaccaride-protein conjugates and whole cell bacteria which elicit antibodies directed against PEtn-containing epitopes, thus anticipating claims directed to a vaccine for pathogenic *Neisseria*, comprising an immunogenic component based on the inner core of an *Neisseria* LPS.

Applicants respectfully disagree. Applicants claim an immunogenic component that consists of an epitope on the *Neisseria* LPS inner core characterized by the presence of a PEtn moiety linked to a 3, 6, 7, or a combination thereof, position of HepII of inner core LPS. Verheul does not demonstrate that the PEtn moiety of LPS is immunogenic. Verheul merely demonstrates antibody responses directed against phosphate containing epitopes. Further, Verheul does not demonstrate that the PEtn moiety of inner core LPS is an exposed epitope. The LPS conjugates of Verheul comprise outer core LPS, which would be expected to mask

reactivity to epitopes in the inner core LPS, therefore one skilled in the art would not accept Verheul as a credible reference that PEtn is the epitope recognized by the antibodies. Moreover, Verheul did not demonstrate that the elicted antibodies are opsonic, bactericidal or in any way protective. Thus, it is not credible, based on Verheul, that a vaccine comprising a phosphoethanolamine moiety linked to a 3, 6, 7, or a combination thereof, position of HepII of the inner core, is useful for the treatment of disease caused by pathogenic *Neisseria*.

Applicants are pursuing the subject matter of the cancelled claims in a subsequent application. Accordingly, Applicants respectfully request withdrawal of the rejection, and allowance of the amended claims.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 05-0649.

Respectfully submitted,

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